REFLEX SYMPATHETIC DYSTROPHY

An Exaggerated Regional Inflammatory Response?

Lyckle van der Laan, MD, and R. Jan A. Goris, MD, PhD

Reflex sympathetic dystrophy (RSD) is a potentially incapacitating syndrome, occurring in an extremity, usually after minor trauma or surgery. Contusions, distortions, and fractures are injuries that may induce RSD. The reported incidence of RSD after fractures is 7% to 37% after a Colle's fracture\(^5\)\(^,\)\(^14\) and 30% after tibial shaft fracture.\(^5\)\(^4\) Minor operations such as carpal tunnel release and arthroscopy may be complicated by RSD.\(^15\)\(^,\)\(^43\) In 10% of patients, RSD develops spontaneously.\(^44\) Early recognition and treatment of RSD are necessary because RSD patients are at risk of severe disability of the affected extremity, eventually resulting in unemployment.\(^5\)\(^1\) We review the history, pathophysiology, and treatment of RSD, with special attention to the role that an exaggerated inflammatory process may play in acute RSD.

HISTORY

In 1864, the signs and symptoms of RSD were first described in detail in soldiers suffering from gunshot wounds inflicted during the Civil War.\(^47\) Mitchell\(^46\) named the syndrome causalgia because of the burning pain in the affected limb. A role for the sympathetic system in the pathophysiology of RSD was first suggested by Leriche in 1916.\(^41\)

Livingston\(^44\) described a "vicious cycle" as an explanation for the pathogenesis of RSD. He theorized that activation of the nociceptors leads to excitation of internuncial pool of neurons of the spinal cord, with induction of increased activity of the efferent sympathetic system. The subsequent vasoconstriction, with ischemia of the tissue, may stimulate the nociceptors, with re-excitation of the spinal cord. Another hypothesis addresses the development of crosstalk between peripheral nerves in an "artificial synapse."\(^18\)

A totally different view on the pathogenesis of RSD was introduced by Sudeck,\(^61\) who described the similarity in symptoms between an inflammatory reaction and RSD. In his last publication,\(^61\) as a professor emeritus at the University of Hamburg, he stated "the hypothetical inflammatory agent is an endogenous pro-inflammatory substance, specifically inducing hyperemia, and is probably related to histamin."

Recently, the "sympathetic" theory was replaced\(^36,\)\(^,\)\(^48,\)\(^55,\)\(^59\) by the hypothesis that an upregulated sensitivity of \(\alpha\)-adrenoceptors

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for catecholamines may induce RSD.\textsuperscript{3, 4, 20, 38, 52} Other hypotheses on the pathogenesis of RSD refer to an involvement of the central nervous system and to an exaggerated peripheral (neuro)inflammatory response to tissue injury.\textsuperscript{50, 56, 69} The numerous synonyms for RSD indicate that a consensus concerning the pathophysiology of RSD is still lacking (Table 1). In 1986, RSD was defined by the International Association for the Study of Pain (IASP) as “continuous pain in a portion of an extremity after trauma, which may include fracture but does not involve a major nerve, associated with sympathetic hyperactivity.”\textsuperscript{32} In 1991, the Ad Hoc Committee of the American Association for Hand Surgery defined RSD as “a pain syndrome in which the pain is accompanied by loss of function and evidence of autonomic dysfunction.”\textsuperscript{22} Recently, the IASP renamed RSD \textit{complex regional pain syndrome} (CRPS) to avoid any mechanistic term in its appellation.\textsuperscript{59} A disadvantage of that denomination is that patients who meet all criteria of CRPS but without pain are excluded. For that reason, we proposed to alter the name to \textit{complex regional dysfunction system}.\textsuperscript{64}

**PATHOPHYSIOLOGY**

**Psychosocial Factors**

Various predisposing psychosocial factors, such as emotional instability, nervousness, depression, anxiety, and certain life events have been linked to the development of RSD.\textsuperscript{22, 23, 65} A critical review of the relevant literature, however, reveals no evidence for predisposing psychosocial factors.\textsuperscript{11, 45} In the only prospective study, performed for this report, 160 patients received a battery of psychological and personality tests 1 day after sustaining a Colles’s fracture.\textsuperscript{66} No difference was found in the results of the tests between patients who eventually did or did not develop RSD.

DeGood et al\textsuperscript{16} compared pain intensity and emotional distress of patients with chronic RSD, low back pain, or headache. They found that RSD patients had the highest level of pain intensity but relatively less emotional distress than the other chronic pain patients.

**Sympathetic Nervous System**

The hypothesis that a hyperactive sympathetic nervous system induces RSD is mainly supported by the presence of hyperhidrosis and vasomotor instability in extremities with RSD and by the reduction of complaints after sympathectomy\textsuperscript{10, 12}—especially the reduction of pain.\textsuperscript{1, 31, 49, 70} Most studies, however, were retrospective. In double-blind randomized studies, no difference was found between sympathetic blockade and placebo treatment.\textsuperscript{9, 33, 53} Recent studies\textsuperscript{20, 21, 54} demonstrated diminished concentrations of norepinephrine and neuropeptide Y in RSD extremities compared with the unaffected side, thereby refuting the theory of a hyperactive sympathetic system in RSD. Those findings have introduced a new view on the pathogenesis of RSD—namely, upregulation in sensitivity of the \(\alpha\)-adrenoreceptors for circulating catecholamines.\textsuperscript{1, 20, 38}

**Inflammatory Response**

Paul Sudeck\textsuperscript{61} proposed that RSD could be caused by an exaggerated inflammatory response after injury or operation of an extremity. In a prospective study by Veldman et al.,\textsuperscript{69} 829 RSD patients were examined for the signs and symptoms of RSD to be diagnosed as RSD, the following criteria were used:

1. At least four of the following five:
   - Unexplained diffuse pain
   - Difference in skin color compared with the other extremity
   - Diffuse edema
   - Difference in skin temperature compared with the other extremity
   - Limited active range of motion
2. Occurrence or increase in the aforementioned signs and symptoms after using the extremity
3. Aforementioned signs and symptoms present in an area larger than the area

**Table 1. SYNONYMS OF REFLEX SYMPATHETIC DYSTROPHY**

<table>
<thead>
<tr>
<th>Causalgia</th>
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<tbody>
<tr>
<td>Algodystrophy</td>
</tr>
<tr>
<td>Post-traumatic dystrophy</td>
</tr>
<tr>
<td>Sudeck's atrophy</td>
</tr>
<tr>
<td>Pourfour du Petit syndrome</td>
</tr>
<tr>
<td>Shoulder-hand syndrome</td>
</tr>
<tr>
<td>Postinfracrational sclerodactyilia</td>
</tr>
<tr>
<td>Complex regional pain syndrome</td>
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</tbody>
</table>
of primary injury or operation and including the area distal to the primary injury.

In acute RSD patients examined within 2 months after the onset of the disease, the signs and symptoms of inflammation were observed (Table 2). From the onset of the disease, neurologic symptoms also were found in the affected limb, such as hypesthesia, hyperpathy, incoordination, tremor, involuntary movements, muscle spasms, and paresthesia. Sympathetic signs were found in only 57% of the acute RSD patients.

In this large population of RSD patients, we could identify a subgroup with the “classical” three-phasic RSD—primarily “warm,” a second phase of vasodilatation, and a late “cold” phase. But a substantial number of RSD patients retained a warm skin temperature for years. In 13% of the acute RSD patients, the skin temperature of the affected extremity was colder than in the healthy contralateral extremity from the onset, considered “primarily cold RSD.” Those findings are in disagreement with the classical subdivision of RSD patients in three stages based on skin temperature. In our view, therefore, the classical subdivision has to be revised to a subdivision of “primarily warm” and “primarily cold” skin temperature at the onset, especially because the last-mentioned group has a worse outcome as to function, a higher incidence of recurrence of RSD, and more frequently requiring amputation.

Because, in 1982, our department of anesthesiology decided not to perform any more sympathetic blockades in acute warm RSD patients, we were left without any meaningful therapeutic option. We therefore started various studies in acute and chronic RSD patients. From our scientific work in acute respiratory distress syndrome, sepsis, and multiple organ dysfunction syndrome, we hypothesized that a regional, exaggerated inflammatory response to injury may induce the early inflammatory and late dystrophic changes in RSD. Various investigations support that view.

NEW INVESTIGATIONS

Arterial Blood Flow, Oxygen Utilization, Tissue Oxygenation, and Lactate Flux

We assessed arterial blood flow and venous oxygen saturation in eight patients with acute warm RSD of one hand. Arterial blood flow was assessed scintigraphically by the left-to-right distribution of technetium-dimethylphosphonate tracer. Venous oxygen saturation (S,O2) was measured via blood samples obtained from the antecubital vein. Arterial flow to the RSD extremity was significantly increased and the S,O2 was extremely high (Table 3).

In one patient, we could perform a flux study of both upper extremities. Arterial flow was assessed by echo Doppler and venous samples were obtained by retrograde cannulation of the antecubital vein. Arterial blood

Table 2. CLINICAL SIGNS AND SYMPTOMS OF ACUTE REFLEX SYMPATHETIC DYSTROPHY IN 156 PATIENTS

<table>
<thead>
<tr>
<th>Inflammatory Signs and Symptoms</th>
<th>Percentage</th>
<th>Neurologic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>92</td>
<td>Hypesthesia</td>
<td>69</td>
</tr>
<tr>
<td>Edema</td>
<td>86</td>
<td>Hyperpathy</td>
<td>75</td>
</tr>
<tr>
<td>Difference in skin temperature</td>
<td>98</td>
<td>Incoordination</td>
<td>53</td>
</tr>
<tr>
<td>Difference in skin color</td>
<td>97</td>
<td>Tremor</td>
<td>54</td>
</tr>
<tr>
<td>Limited range of motion</td>
<td>90</td>
<td>Involuntary movements</td>
<td>19</td>
</tr>
<tr>
<td>Increase in complaints after exercise</td>
<td>98*</td>
<td>Muscle spasms</td>
<td>11</td>
</tr>
<tr>
<td>Paresis</td>
<td></td>
<td></td>
<td>98</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Atrophy</th>
<th>Percentage</th>
<th>Sympathetic</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin</td>
<td>38</td>
<td>Hyperhidrosis</td>
<td>57</td>
</tr>
<tr>
<td>Nails</td>
<td>15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients examined within 2 months after its onset.44

*Note: the remaining 2% of patients were unable to exercise the affected limb at all.

Table 3. VENOUS OXYGEN SATURATION AND ARTERIAL BLOOD FLOW DISTRIBUTION IN ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY AND IN HEALTHY UPPER EXTREMITIES (n = 8)

<table>
<thead>
<tr>
<th></th>
<th>RSD (%)</th>
<th>Healthy (%)</th>
<th>Difference (%)</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous oxygen saturation</td>
<td>86.5</td>
<td>68.7</td>
<td>17.8 ± 4.6</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>Arterial flow</td>
<td>69.4 ± 7.4</td>
<td>30.6 ± 3.1</td>
<td></td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

gas and lactate samples were obtained from the femoral artery. Again, S\textsubscript{O\textsuperscript{2}} and arterial flow were high whereas oxygen consumption and oxygen extraction were low. Despite a high oxygen supply, the lactate in the RSD extremity was increased by a factor of five (Table 4). This increased lactate flux despite elevated arterial blood flow in RSD limbs indicates tissue hypoxia and is caused either by cellular intoxication with impaired oxygen utilization or by an oxygen diffusion problem between the arterioles and mitochondria. In any case, the data obtained in this study indicated tissue hypoxia despite supranormal arterial oxygen supply in extremities with acute RSD. This odd combination of high oxygen supply and tissue hypoxia seems to be found consistently in areas affected by severe inflammation, burn injury, varicose ulcers, malignant tumors, ischemia/reperfusion, and in feet affected by diabetes mellitus.\textsuperscript{25}

Phosphorus 31 Nuclear Magnetic Resonance Spectroscopy

Phosphorus 31 nuclear magnetic resonance spectroscopy (\textsuperscript{31}P-NMR) is a noninvasive technique to measure the high-energy phosphate compounds of skeletal muscle. It is applied in investigations of various human metabolic skeletal muscle disorders. By analyzing the spectra obtained, it is possible to assess the concentrations of substrates necessary for skeletal muscle activity, such as adenosine triphosphate (ATP), phosphocreatine (PCr), and the degradation product inorganic phosphate (Pi). During skeletal muscle exercise, PCr is consumed for the resynthesis of ATP, whereas resynthesis of PCr (from anorganic phosphate and creatine) is oxygen dependent. Under ischemic or hypoxic conditions, therefore, cellular ATP cannot be resynthesized by oxidative phosphorylation.

We applied the technique in 11 chronic RSD patients whose legs were affected.\textsuperscript{30} \textsuperscript{31}P-NMR spectra were obtained at the level of the calf muscle in a 1.5-Tesla NMR apparatus and were compared with the spectra of the healthy limbs. The Pi:PCr ratio in the RSD limbs was 0.24 ± 0.02, whereas that in the healthy control limb was 0.13 ± 0.02 (P<0.01). That finding indicates diminished oxygen availability to the tissue in these late, severe cases of RSD.

One young (21 years) male patient, who had no signs of RSD when using free-radical scavenger treatment (explained in the section on another approach to treatment) and who had returned to work, complained of paresis and relapse of RSD symptoms in his hand whenever he stopped taking his medication. We could obtain \textsuperscript{31}P-NMR spectra of the thenar muscles of both hands 2 weeks after stopping his medication. Spectra were obtained before, directly after, and 2 minutes after exercises consisting of pumping a sphygmomanometer to a predetermined level (Fig. 1). Measurements were performed with a 6.3-Tesla magnet at the Philips Physics Labora-

Table 4. FLUX STUDY IN FEMALE PATIENT (52 YEARS OLD) WITH ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY OF THE RIGHT HAND*  

<table>
<thead>
<tr>
<th></th>
<th>RSD Hand</th>
<th>Healthy Hand</th>
</tr>
</thead>
<tbody>
<tr>
<td>Venous lactate concentration</td>
<td>1172 mmol/L</td>
<td>783 mmol/L</td>
</tr>
<tr>
<td>Arterial lactate concentration</td>
<td>630 mmol/L</td>
<td>630 mmol/L</td>
</tr>
<tr>
<td>Arterial flow (via echo Doppler)</td>
<td>160 mL/minute</td>
<td>125 mL/minute</td>
</tr>
<tr>
<td>Lactate flux</td>
<td>86.7 mmol/minute</td>
<td>19.1 mmol/minute</td>
</tr>
<tr>
<td>Oxygen extraction factor</td>
<td>0.19</td>
<td>0.31</td>
</tr>
<tr>
<td>Oxygen consumption</td>
<td>30.4 mL O\textsubscript{2}/minute</td>
<td>39 mL O\textsubscript{2}/minute</td>
</tr>
</tbody>
</table>

*Performed by bilateral retrograde cannulation of the antecubital vein.
Figure 1. A $^{31}$P NMR spectra of healthy (A, B, D) and RSD (C, E) hand in a 21-year-old patient (see text) before, during, and after exercise of the hand. The first peak is inorganic phosphate (Pi), the second peak phosphocreatine (PCr), the three following peaks three phosphor groups of adenosine triphosphate (ATP). A, The $^{31}$P NMR spectrum of the healthy hand at rest. B, $^{31}$P NMR spectrum of the healthy hand during exercise. C, Directly following exercise, PCr has almost disappeared in the affected hand while Pi is strongly increased. D, $^{31}$P NMR spectrum after 2 minutes of exercise of the healthy hand. E, Two minutes after exercise PCr increases and Pi decreases but not as far as in the healthy control hand.
tory in Eindhoven. Upon exercising, we could demonstrate a quick and profound drop in skeletal muscle PCr, followed by slow recovery at rest (see Fig. 1).

These observations with 31P-NMR, in particular, convinced us that RSD patients are unable, rather than unwilling, to exercise.

**Indium-111-Immunoglobulin G Scintigraphy**

Indium-111-immunoglobulin (In-111-IgG) scintigraphy is an established technique for recognizing infectious and inflammatory lesions by accumulation of the labeled high-molecular-weight immunoglobulin in the affected area. The extravasation of In-111-IgG is caused by increased vascular permeability for macromolecules as a result of inflammatory damage to the vascular endothelium. In-111-IgG scintigraphy was performed in 23 patients with RSD of one hand. In 17 patients, RSD was present for less than 5 months; in six patients, for longer than 5 months. Images were obtained by a gamma camera, immediately, 5 minutes after, and 4, 24, and 48 hours after intravenous injection of In-111-IgG. The uptake of In-111-IgG was expressed as the uptake ratio between the affected and unaffected hands. In the acute phase of RSD, 14 of 17 RSD patients had a progressive accumulation of the labeled immunoglobulin in the affected hand (Fig. 2) independent of the arterial flow. In chronic RSD patients, the scintigrams were normal in five of the six patients. From that study, it was concluded that, in acute RSD, extravasation of macromolecules is present in the affected area, indicating a regional inflammatory process.

**Histology**

Obtaining tissue from an RSD patient for histologic analysis is difficult because any additional injury may trigger an increase of severity or recurrence of RSD. For that reason, we performed biopsies only in chronic, severe RSD cases. Biopsies were taken from the gastrocnemius muscle of RSD-affected legs. Duration of RSD varied from 12 to 46 months. Analysis by light microscope showed extreme accumulation of lipofuscin in the skeletal muscle of RSD patients. Lipofuscin is a degeneration product, produced during lipid peroxidation of the cellular membrane. With age, the amount of lipofuscin in tissue increases slowly. In the gastrocnemius muscle of RSD patients, the amount of lipofuscin observed was clearly increased compared with the gastrocnemius muscle of persons of the same age but without RSD (Fig. 3). On electron microscope, sarcomer blebbing, swelling, and vesiculation of the mitochondria; disintegration of myofibrils, and Z-band irregularities were observed in the skeletal

![Figure 2](image-url). Indium-111-IgG scintigraphy of a RSD patient. RSD developed after contusion of the left hand, 3 months prior to the scintigraphy. The left scintigram shows both hands 5 min after In-111-IgG injection, the right scintigram 24 h after injection. The right scintigram shows accumulation (arrow) of In-111-IgG in the affected hand by RSD.
muscle of chronic RSD patients. Those cellular abnormalities could be provoked by oxidative stress.

**Anti-Inflammatory Therapy**

In a prospective, placebo-controlled study, Christensen et al demonstrated that corticosteroids significantly decrease the complaints of RSD. Unfortunately, the corticosteroid dosages have to be 20 to 100 mg daily for long periods, which may induce deleterious side effects.

Based on the hypothesis that RSD is an exaggerated inflammatory response, we evaluated free-radical scavengers as treatment of acute RSD. The approach was suggested by recent knowledge that free radicals are generated during inflammatory processes and induce tissue damage. Treatment consisted of low-dose continuous intravenous infusion of mannitol or local application of dimethyl sulfoxide (DMSO). In a crossover study, DMSO had a significantly better result than placebo (Fig. 4). The therapeutic effects of local DMSO application in acute RSD were confirmed by two other studies, an open study by Langendijk et al and a study by Geertzen et al comparing DMSO to intravenous isomelin blocks.

We also assessed the effects of 1 week of intravenous mannitol treatment on arterial flow and oxygen extraction in patients with severe acute warm RSD of one upper extremity (Table 5). Besides important improvement in clinical signs and symptoms of acute inflammation, the mannitol significantly decreased arterial flow and $S_O_2$ saturation, indicating improved tissue extraction.
Neuroinflammatory Mediators

It is known from various animal studies that bradykinin, substance P (SP), and calcitonin gene-related peptide (CGRP) provoke an inflammatory reaction with hyperalgesia in a hindlimb. Schwartzman and Kerrigan suggested that SP may have an important role in the pathogenesis of the neurologic-complication dystonia in RSD patients, and Schott hypothesized that SP and CGRP are involved in the inflammatory reaction and the accompanying motor and sensor disturbances of RSD. Analysis of blood samples obtained from 61 RSD patients showed significantly increased systemic levels of bradykinin and CGRP compared with 21 controls.

Experimental Model

We developed an animal model that allows for continuous intra-arterial infusion of the free radical donor tert-butylhydroperoxide (tert-BuOOH) or a placebo in one hindlimb of nonanesthetized rats. In placebo-infused rats, no measurable signs of inflammation were found in the infused paw. In the tert-BuOOH-infused hindlimbs, we found increased skin temperature, edema, redness of the skin, impaired function, spontaneous pain behavior, and increased sensitivity to mechanical and thermal pain stimuli (Fig. 5). Those signs and symptoms are similar to those found in acute RSD patients. In addition, the observed pain sensations in the free
Figure 4 (Continued).

Figure 5. Feet of a rat after 24 h infusion with a free radical donor. The infused foot (right) is clearly swollen and has a red color, but the control foot is unaffected.
radical-infused animals were similar to the pain sensations present in an animal model of neuropathic pain currently used as a model of RSD. In contrast to the neuropathic animal model, in which the pain sensations appear 5 days postoperatively, in our animal model, the pain sensations are present within 24 hours of infusion.

### ANOTHER APPROACH TO TREATMENT

During the last 15 years, we progressively adapted our treatment schedule for RSD to new knowledge and increasing experience. During that period, we examined more than 1500 RSD patients, 90% of them referred from other clinics. Our present approach is summarized here.

### Free-Radical-Scavenger Treatment

In 1982, we started treating acute RSD patients with free-radical scavengers. Patients with severe, acute RSD are treated with intravenous mannitol (10%, 1 L/24 hours) for 1 week. Care should be taken in patients with renal failure because hyperosmolality may occur. When renal function is normal, osmolality is not increased significantly.

Subsequently, the patients are treated with application of DMSO cream (50%) on the skin of the affected area five times daily for approximately 2 to 3 months.

Less severe cases of RSD are treated initially with DMSO cream.

### Vasodilation Treatment

The decreased arterial flow found in “primarily cold” RSD probably contributes to the worse outcome found in that subgroup. “Primarily cold” RSD patients therefore, are treated early and rigorously with vasodilators such as verapamil (one or two times, orally, 240-mg sustained release/24 hours), ketanserin (two times orally, 20 or 40 mg/24 hours), or pentoxyfiline (one or two times, orally, 400 mg/24 hours) to optimize perfusion of the affected extremity. When the skin temperature remains cold despite the vasodilators, sympathetic blockade is performed at an early stage.

### Attention to Painful Trigger Points

In about 50% of RSD patients, a “trigger point” is present. A trigger point is defined as a specific painful area within the affected RSD extremity in which the pain is not directly caused by RSD. Examples are tendinitis of the tendons of one or both biceps muscles, epicondylitis lateralis or medialis, carpal tunnel syndrome, neuroma, trigger finger, anterior metatarsalgia, “jumper knee,” or tendinitis of the patella tendon. Our hypothesis is that these trigger points may induce, sustain, or worsen RSD, possibly by a local process of neurogenic inflammation. During the treatment of RSD, the trigger points are identified and given specific treatment, which may include the operative removal of a neuroma, local injection of bupivacaine followed by methylprednisolone for tendinitis, or use of an orthosis for immobilization of a painful joint.

### Physical Therapy?

Muscular work is accompanied by an increase in oxygen consumption, and may induce free-radical production. In addition, it is almost pathognomonic of RSD patients that muscular work of the affected extremity induces or increases the inflammatory signs and symptoms, especially pain, within the affected extremity. For that reason, we advise RSD patients to actively exercise their affected extremity, but within their pain

### Table 5. VENOUS OXYGEN SATURATION AND ARTERIAL BLOOD FLOW DISTRIBUTION IN ACUTE WARM REFLEX SYMPATHETIC DYSTROPHY UPPER EXTREMITIES (n = 8), BEFORE AND AFTER 1 WEEK OF LOW-DOSE INTRAVENOUS MANNITOL

<table>
<thead>
<tr>
<th></th>
<th>Before (%)</th>
<th>After (%)</th>
<th>Difference (%)</th>
<th>Significance</th>
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<tbody>
<tr>
<td>Venous oxygen saturation</td>
<td>86.5</td>
<td>80.1</td>
<td>6.4 ± 2.8</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Arterial flow</td>
<td>69.4 ± 7.4</td>
<td>62.9 ± 5.6</td>
<td>6.5 ± 4.9</td>
<td>P = 0.012</td>
</tr>
</tbody>
</table>
Reflex Sympathetic Dystrophy with Severe Disability

Some cases of RSD are resistant to any of the presently known modes of treatment. In such patients, a completely different approach is necessary, addressing their severe disability. Such an approach should include providing an orthosis, a wheelchair, and adoption of their home situation, as appropriate.

CONCLUSION

How do these findings fit with the hypothesis that an exaggerated inflammatory response is involved in the pathogenesis of RSD? The scintigraphic study demonstrated vascular leakage for macromolecules in the acute phase of RSD, such as is found in inflammatory processes. Impaired oxygen extraction, also found in acute RSD-affected extremities, is another phenomenon detectable in areas of inflammation. In chronic RSD patients, the increased Pi/PCr ratios at rest indicate a change in the energy balance of the affected tissue. Infusion of free radicals in a hindlimb of a nonanaesthetized rat mimics the acute signs and symptoms of RSD. During inflammatory- and hypoxia-related processes, free radicals are generated. In biopsies of chronic RSD cases, increased lipofuscin is found, indicating oxidative stress. Treatment of RSD patients with free-radical scavengers reduces the signs and symptoms of this syndrome, while increasing oxygen extraction.

All these findings support the hypothesis that RSD is the result of an exaggerated inflammatory response to injury or operation.

ACKNOWLEDGMENTS

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